IN THE CLAIMS

Amend claim 32 as follows:

32. (Twice Amended) A cosmetic or dermatological formulation comprising:

a) one or more flavonoids selected from the group consisting of alpha-glucosylmyrictrin, alpha-glucosylisoquercitrinin, alpha-glucosylquercitrin, myricetin, rhamnetin, apigenin, hesperitin, morin, phloridzin, diosmin, vitexin, neohesperidin dihydrochalcone, flavone, and genistein;

b) optionally one or more cinnamic acid derivatives; and

c) optionally an antioxidant.

34. (New) A cosmetic or dermatological formulation comprising:

a) one or more flavonoids selected from the group consisting of alpha-glucosylmyrictrin, alpha-glucosylisoquercitrinin, alpha-glucosylquercitrin, myricetin, rhamnetin, apigenin, hesperidin, hesperitin, morin, phloridzin, diosmin, vitexin, neohesperidin dihydrochalcone, flavone, glucosylrutin and genistein;

b) one or more cinnamic acid derivatives; and

c) one or more antioxidants.

CONDITIONAL PETITION FOR EXTENSION OF TIME

If any extension of time for this response is required, Applicants request that this be considered a petition therefore. Please charge the required fee to Deposit Account No. 14-1263.

ADDITIONAL FEES

Please charge any further insufficiency of fees, or credit any excess to Deposit Account No. 14-1263.

REMARKS

Entry of the amendment and consideration of the remarks is respectfully requested.

The amendment of claim 32 overcomes the anticipation by Suzuki. The amendment, does not raise new issues or add new matter.

New claim 34 is rejected claim 32, wherein the additional components are not recited as optional. New claim 34 is not anticipated by Suzuki or by Raff.

It is respectfully suggested that considering the remarks is appropriate, in view of the fact that these remarks indicate that a proper interpretation of Middleton requires that the rejections under § 103 be withdrawn.

It will be pointed out below with particularity, that Examiner has not properly interpreted the teachings of Middleton in general, as well as the specific portions cited in the rejections.

Claims 19-33 are pending in the application.

Claims 32-33 are rejected as allegedly being anticipated by US '781 to Suzuki.

Claims 25-31 are rejected as allegedly being anticipated by US '912 to N'Guyen.

Claims 19-29 are rejected as allegedly being obvious over US '171 to N'Guyen in view of Middleton and Harrison.

Claims 19-33 are rejected as Examiner believes the claims unpatentable for obviousness-type double patenting over claims 1 and 4 of US '373 and claims 1-5 of US

'243. Claims 19-33 are provisionally rejected on the same basis in view of Applications 09/656598 and 09/540007.

Claims 32-33 are rejected as allegedly being anticipated by US '343 to Raff.

The rejections will be addressed in the sequence they were presented in the final action.

Preliminary Remarks in Response to Examiner's Comments

In the final action, as well as in the office action of May 22, 2002, Examiner applies the article of Middleton for demonstrating the state of the art. However, Examiner has inaccurately interpreted the teachings of Middleton, and in so doing, has not properly combined it with N'Guyen and Harrison.

It is indisputable that the sum total of Middleton's discussion of the effects of flavonoids on T-cell activity predicts that flavonoids would suppress T-cell function, and *therefore enhance immunosuppression*. As such, Middleton's disclosure (pp. 625-628) teaches away from (1) the claimed method, and (2) Examiner's interpretation of the combined teachings of N'Guyen, Harrison and Middleton.

In the office action of May 22, 2002, Examiner correctly, albeit selectively, refers to Middleton's teaching that genistein inhibits T-lymphocyte protein tyrosine kinase activity. See office action, page 8. However, Examiner then apparently and incorrectly concludes that such stimulation leads to immunosuppression, while Middleton concludes the opposite.

Perhaps Examiner believes the reference to T-cells to mean only T suppressor cells. This is incorrect in view of the fact that persons with skill in the art would specify if T suppressor cells were being discussed – as did Harrison, page 309-10. Also, in the context of the entire section in Middleton, it is clear that the overwhelmingly major portion of the data presented points toward flavonoids actually augmenting immunosuppression.

A portion of these data are presented below.

- Genistein inhibits the protein kinase, p56^{lck}, thus inhibiting T-cell stimulation as evidenced by reduced interleukin production. Reducing cytokine production is known to diminish the immune response and, therefore, enhances immunosuppression. Page 625, col. 2, 1st paragraph.

- Genistein was explicitly disclosed as having immunosuppressive properties in experiments relating to graft rejection reactions. Page 625, col. 2, 2nd paragraph. Middleton concludes "[t]he potential use of genisteinn as an immunosuppressive agent together with cyclosporine in allograft rejection was suggested."

- Quercitin inhibits another protein tyrosine kinase found in human plasma. Page 625, col. 2, 3rd paragraph

- PI kinase, an enzyme that generates phosphatidyl inositolphosphates as second messengers involved in T-cell activation, can be inhibited by various flavonoids. See Page 626, col. 1, 1st paragraph. Inhibiting T-cell activation is very likely to lead to immunosuppression.

- Protein kinase C, known to be involved in T-cell activation is inhibited by flavonoids. Page 626, col. 1, 2nd paragraph. Inhibiting T-cell activation is very likely to lead to immunosuppression.

- Middleton discloses that several downstream effectors in T-cells may be inhibited by flavonoids. Page 626, col. 1, 3rd paragraph. Thus, inhibiting T-cell function enhances immunosuppression.

- Flavonoids blocked activation of T-cells via the CD3 T-cell Receptor. Page 626, col. 2, 2nd paragraph. One in the art would understand that inhibition of T-cell activation may lead to immunosuppression.

- Flavonoids depressed the expression of class II histocompatibility antigens. Page 627, col. 1, 1st paragraph. This clearly enhances immunosuppression by inhibiting antigen presentation to T-cells, and thus, block T-cell activation.

- Flavonoids inhibit lymphocyte proliferation in response to mitogens. Inhibiting lymphocyte proliferation clearly promotes immunosuppressive effects. Page 627, col. 1, 1st paragraph.

- Various flavonoids have been shown to inhibit the development of cytotoxic lymphocytes as well as their specific functions. Page 627, col. 2, 2nd paragraph.

- Flavonoids inhibited the immune response to sheep erythrocytes *in vitro*. Page 627, col. 1,3rd paragraph.

- Various flavonoids inhibit spleen cell proliferation in response to T-cell presentation of a mitogen. Page 627, col. 1,3rd paragraph.

- A unique flavonoid inhibited various mitogen-induced effects on various cells of the immune system. Page 627, col. 1,3rd paragraph.

In view of this, it is suggested that Examiner's acknowledgement of Middleton's "plethora of information about the effects of flavonoids on the immune system" (office action 5/222002, page 8) was not properly interpreted.

Persons of ordinary skill in the art could not reasonably have been expected to view flavonoids as counteracting immunosuppressive condition. Thus, combining Middleton and Harrison cannot properly be combined with N'Guyen to reject the claims.

Examiner's interpretation of the scientific data must also be called into question with respect to her citing of Okada et al.

Examiner attempts to support her position by citing work by Okada et al., in Middleton, page 627, 2nd col.[sic] (should be first column) that shows "quercitin has been effective in regressing the spread of fibrosacroma." Office action, 5/22/2003, page 8. However, if the relevant text is read in its entirety, it clearly states that it was the fibrosarcoma cells that were treated with quercitin, not the T-lymphocytes or the mice. Consistent with this is Okada's disclosure that the flavonoids-treated fibrosarcoma cells

were cloned out, and that quercitin apparently induced new fibrosarcoma clones having different immunological properties. Page 627, bottom of col. 1.

Most important is that this is a case where quericitin, again, *stimulates* immunosuppression. However, in this experiment, the immunosuppressive effect was due to the flavonoid's effects on the cancer cells themselves, and not the immune system. Thus, Okada also teaches the opposite of the claimed method. It is critical to appreciate that Okada also directly contradicts Examiner's rationale based on combining N'Guyen and Harrison (discussed below).

In the same office action, Examiner asserts that "topical quercitin has been effective in preventing and improving various immunosuppressive conditions associated with skin cancer (see pp 642, 3rd-8th)." This statement has no basis in any explicit or implied facts in the cited text.

- The cited text does not even discuss immune responses at all. Examiner's belief that all tumors grow due to immunodeficiency is not accepted in the art, and is not disclosed here.

- An even cursory reading would have indicated that the proposed mechanisms for these effects *did not relate to immunology at all*. The proposed explanations ranged from not knowing, to effects on enzyme systems that are known to activate chemical carcinogens; most notably the P-450 family.

The misinterpretation of Middleton's summary of the art is key in maintaining the rejections, and is also critical in arguing in support for their withdrawal. It is respectfully requested that Examiner consider the foregoing remarks when evaluating the comments in support of withdrawing the rejections.

Anticipation by 781 to Suzuki

In the final action, Examiner correctly states that claims 32-33 encompass a cosmetic or dermatologic composition comprising glucosylrutin. Final action, section 3.

In response, Applicants have amended claim 31, by deleting *glucosylrutin*. Accordingly, Suzuki does not anticipate claims 31 and dependent claim 32.

Anticipation by 912 to N'Guyen

Examiner Asserts an Undisclosed and Unsupported Scientific Theory to Maintain the Rejection

The Examiner indicates that the '912 explicitly discloses topical application of N'Guyen's compositions to protect the skin from oxidation, and therefore anticipates the claims. See final action, section 7. Respectfully, this argument is not logical or technically sound, and therefore, is not legally sufficient to maintain the rejection. **MPEP § 2144.02.**

The cited text (col. 5, lines 59-61) expressly states that topical applications of N'Guyen's compositions, in particular in cream form, are "intended to protect the lipids of the skin from oxidation." In no way can this intended effect conceptually or medically linked to the claimed method of preventing immunosuppression.

Examiner apparently assumes without evidence or sound technical reasoning, that oxidation of lipids in the skin results in immunosuppression. N'Guyen does not disclose this. Further, neither Harrison nor Middleton fill this gap.

N'Guyen does not the term "immunosuppression" or immuno-anything. Thus, it is not proper to assert N'Guyen' composition as anticipating method claims for treating immunosupporession.

Examiner seems to assert her own theory that immunosuppression results from lipid oxidation. The MPEP explicitly requires that "evidentiary support for the existence and meaning of that theory must be provided." *In re Grose*, 201 USPQ 57 (CCPA 1979). Without such evidence, the basis for rejecting the claims is not supported. **MPEP § 2144.02.**

In view of the complete omission of the subject of immunosuppression by N'Guyen, it is not plausible that any aspect of his disclosure anticipates claims for the treatment of immunosuppression.

Withdrawal of the rejections under § 102 are respectfully requested.

Examiner Apparently Relies on an Inherency Theory

In view of the lack of support for the existence of a connection between lipid oxidation in the skin and immunosuppression, Examiner may believe that topical application of N'Guyen's cream will inherently prevent immunosuppression. If so, it is respectfully pointed out that the legal standard for rejecting claims on an inherency theory is quite clear.

"In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." Ex parte Levy, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (Emphasis added). MPEP § 2112.

"To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' " *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999). MPEP § 2112. (Emphasis added).

It is clear that in order for N'Guyen to anticipate the claims, Examiner must supply evidence demonstrating that her proposed treatment with N'Guyen's cream would necessarily have produced an anti-immunosuppression effect. It is suggested that no such evidence was presented. Further, as discussed below, no such evidence was available at the time of Applicants' filing date.

Applicants respectfully point out the foregoing discussion of Middleton's article, to indicate that any notion that flavonoids necessarily result in immunosuppression cannot be correct.

In accordance with the foregoing remarks, Applicants respectfully request withdrawal of all anticipation rejection over the '912 patent to N'Guyen.

N'Guyen's Disclosure Does not Enable the Claimed Method

It is well established that a proper reference under 35 USC§§102 or 103 must be enabling in the sense of 35 USC § 112, paragraph 1. It is suggested that the '912 to N'Guyen reference is not enabling to that extent. Pertinent is the following quote from *In re Le Grice*, 133 USPQ 365, 374 (CCPA 1962):

> The proper test of a description in a publication as a bar to a patent as the clause is used in section 102(b) requires a determination of whether one skilled in the art to which the invention pertains ***could take the description of the invention in the printed publication and combine it with his own knowledge of the particular art and from this combination be put in possession of the invention*** on which a patent is sought." [Emphasis added]

35 U.S.C. 112 requires the specification to be enabling only to a person "skilled in the art to which it pertains, or with which it is most nearly connected." In general, the pertinent art should be defined in terms of the problem to be solved rather than in terms of the technology area, industry, trade, etc. for which the invention is used. MPEP § 2164.06.

Applicants respectfully point out that it is not reasonable to assert N'Guyen under § 102 as inherently anticipating claims 25-31, because he does not provide any disclosure that would place the claimed method of treating or preventing immunosuppression in the public domain. Therefore, if the claimed method is interpreted in terms of the problem to solved, as the MPEP requires, it is clear that N'Guyen cannot reasonably be found to anticipate the claims.

Applicants respsectfully request withdrawal of the anticipation rejection over N'Guyen's 912.

Obviousness Over '171 to N'Guyen in View of the Articles by Middleton and Harrison

N'Guyen's disclosure is directed to finding alternatives to ascorbate as an antioxidant to prevent oxidation of lipid-containing cosmetic and dermatological formulations. In other words, he is primarily concerned with preserving the product's properties during storage; i.e., to increase its shelf-life. See N'Guyen '171, col. 1 lines 12-53. Among the problems disclosed are oxidation associated changes in the aromatic/olfactory properties (line 17) and, general preservation during storage (lines 42-45). N'Guyen then also discusses the potential benefits to prevent oxidation of skin lipids. Col. 1 lines 54-58.

Although N'Guyen discloses a potential benefit to the skin by preventing lipid oxidation, it is a grossly unjust reading of this reference and unsupported leap of logic for Examiner to suggest that N'Guyen '171 even remotely or impliedly discloses any benefits to the immune system. Final action, page 5-6.

Further, as discussed at length with respect to Middleton's disclosure of the art, persons of ordinary skill could not read the combined references and extract the conclusion that N'Guyen's compositions could attenuate immunosuppression, with a reasonable expectation of success.

After a brief discussion of N'Guyen's disclosure, Examiner asserts that "one of ordinary skill in the art would deduce that topical or cosmetic application of N'Guyen's compositions would provide antioxidizing effects including protecting the lipids of the skin. *Thus, protecting lipid of the skin from oxidation and subsequent damage would attenuate immunosuppression* to the extent that it falls within the scope of the instant pending claims." Final action, page 5. Examiner's rationale seems based more on her own theory of immune suppression than what is disclosed in the references.

Middleton clearly indicates that extrapolating from N'Guyen's disclosure that flavonoids may inhibit the oxidation of skin lipids, to result in the attenuating of immunosuppressive conditions, is to ignore the bulk of evidence to the contrary. Such a

connection cannot be found in any of the references including N'Guyen, Middleton and/or Harrison, and therefore is not a theory known in the art.

Examiner also asserts that the only teachings lacking by N"Guyen is "an explicit statement about beneficial effects of flavonoids on the immune system." Final action, top page 6. This is not correct and further mischaracterizes N'Guyen's disclosure. There is not even an implicit statement about the effects of topically applied flavonoids on the immune system. Examiner's mere belief that lipid oxidation *necessarily* effects the immune system is unsupported speculation that is not within the prior art and cannot be a basis to maintain a rejection.

Just as important, the teachings of Middleton and Harrison cannot fill the missing gaps.

The Combined References Teach Away From Each Other as Well as the Claims

A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 220 USPQ 303 (Fed. Cir. 1983). MPEP § 2141.02.

In addition, "***references cannot be combined where reference teaches away from their combination.***" **MPEP § 2145.** It is improper to combine references where the references teach away from their combination. *In re Grasselli*, 218 USPQ 769, 779 (Fed. Cir. 1983)

Proceeding contrary to accepted wisdom is evidence of nonobviousness. **MPEP § 2145.** The totality of the prior art must be considered, and proceeding contrary to accepted wisdom in the art is evidence of nonobviousness. *In re Hedges*, 783 F.2d 1038, 228 USPQ 685 (Fed. Cir. 1986).

Examiner's rationale for maintaining the rejection under 103 seems to be that Harrison discloses the etiology of UV exposure to immunosuppression, and in so doing supplies the vital link between N'Guyen and immunosuppression, i.e., the claimed method. Final action, page 6. Examiner further states that "Middleton is merely used to show the general knowledge available in the art for the benefits of topical flavonoids in improving immunosuppressive conditions regardless of their etiology." *Id.*

However, as discussed in detail, Middleton explicitly teaches that the major suggestion of the available evidence indicated that flavonoids were thought to enhance immunsuppression, not have anti-immunosuppressive effects. Middleton, page 625, col. 2, 2nd paragraph.

Thus, Middleton indisputably demonstrates that the conceptual state of the art as to the potential effects of flavonoids on immunesuppression was ***stimulatory***. Therefore, based on Examiner's admitted reliance on Middleton, the claimed method of enhancing immunosuppression cannot reasonably be viewed as being obvious over the prior art. The Applicants have *proceeded contrary to accepted wisdom, thus their claimed method is evidence of nonobviousness*. **MPEP § 2145.**

In addition, Examiner has asserted that "Harrison and Middleton bridge the implicit teachings of N'Guyen." This is legally incorrect in view of a fair reading of Middleton and N'Guyen. *These references cannot be combined because Middleton teaches away from its combination with Harrison and N'Guyen's allegedly implied teachings*." **MPEP § 2145.**

In sum, the applied references clearly teach away from their own combination, as well as from the claimed method. It is indisputable that Middleton's summary of the experiments demonstrating that T-cell function are adversely affected by flavonoids, would not reasonably be expected to provide a motivation to combine the references with a reasonable expectation of success in developing immunosuppressive compositions.

In accordance with the Patent Office's procedural rules and guidelines, it is respectfully requested that the rejections under § 103 be withdrawn.

Double Patenting

A terminal disclaimer and an associate power of attorney have been mailed separately.

New Ground for Rejection – Anticipation Over Raffi

This rejection has been overcome by the foregoing amendment.

Claim 32 no longer recites hesperidin.

New claim 34 requires at least one cinnamic acid derivative and at least one non-flavonoid anti-oxidant.

CONCLUSIONS

Allowance of the claims is respectfully requested.

The Middleton reference clearly indicates that the role of flavonoids in immunosuppression as applied by the Examiner is inaccurate. The overwhelming majority of disclosed results indicates that flavonoids are likely to act by enhancing immunosuppression. Thus, Middleton teaches away from both the claims as well as the combination of references.

Respectfully Submitted,

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MARK UP OF AMENDED CLAIMS

32. (Twice Amended) A cosmetic or dermatological formulation comprising:

a) one or more flavonoids selected from the group consisting of alpha-glucosylmyrictrin, alpha-glucosylisoquercitrinin, alpha-glucosylquercitrin, myricetin, rhamnetin, apigenin, ~~hesperidin~~, hesperitin, morin, phloridzin, diosmin, vitexin, neohesperidin dihydrochalcone, flavone, ~~glucosylrutin~~ and genistein;

b) optionally one or more cinnamic acid derivatives; and

c) optionally an antioxidant.